Markers for interferon responsiveness in MS

By Kai-Jye Lou, Staff Writer

Although β-interferons are standard of care for relapsing-remitting multiple sclerosis, with global sales totaling more than $6 billion in 2009, the drugs don't work in about 20% to 25% of patients. Researchers at **Stanford University** and **The University of Alabama at Birmingham** have identified cytokine markers in the blood that predict responsiveness to interferon-β therapies[1] and could lead to a simple blood-based test that would differentiate responders from nonresponders.

"Right now, treatment responsiveness in relapsing-remitting multiple sclerosis is assessed by putting patients on one of the available drugs and seeing empirically whether or not they do well," said Lawrence Steinman, professor of neurology and chairman of the immunology program at Stanford. "There is no clear rationale as to whether a patient with RRMS should be started on β-interferon or another drug [such as] Copaxone."

Copaxone glatiramer acetate is a selective major histocompatibility complex class II (MHCII) modulator. **Teva Pharmaceutical Industries Ltd.** markets it in the U.S. to treat RRMS and shares European rights with **sanofi-aventis Group**.

Profiling cytokine markers in blood serum, said Steinman, should enable us to remove the guesswork. His group used two experimental autoimmune encephalitis (EAE) mouse models, which are used as proxies for MS in humans, to show that responsiveness to interferon-β (IFNB; IFN-β) varies depending on whether the disease is induced by T helper type 1 (Th1) or Th17 cells.

Th17 cells secrete the proinflammatory cytokines IL-17A and IL-17F (ref. 2), whereas Th1 cells do not.

In mice with Th1-induced EAE, IFN-β treatment significantly reduced disease severity compared with controls ($p<0.05$). In contrast, IFN-β treatment significantly increased disease severity in mice with Th17-induced EAE compared with controls ($p<0.05$).

"One of the main implications of this work is that RRMS may come in more than one variety—one driven by Th17 cells, which does not respond to β-interferon, and one driven by Th1 cells, which does respond," Steinman told *SciBX*.

In a cohort of 26 RRMS subjects with MS, including 14 IFN-β nonresponders, analysis of serum cytokines showed that six of the nonresponders had significantly elevated IL-17F compared with responders ($p<0.001$).

"We've also found other markers that could help predict responsiveness to β-interferon, one of which is endogenous β-interferon itself," said Steinman. "We found that the level of IL-17F correlates closely with β-interferon levels. But whether it's β-interferon driving IL-17F or IL-17F driving β-interferon is not known at this point."

Indeed, the six nonresponders with elevated IL-17F also had significantly higher endogenous IFN-β levels than did responders ($p<0.002$).

The findings were published in *Nature Medicine*.

Steinman, who is a co-corresponding author on the paper, said the cytokine profiling study "was able to capture about 50% of the nonresponders." His group "is now evaluating a more sensitive version of the test that captures about 80% of the nonresponders."

Chander Raman, an associate professor in clinical immunology and rheumatology at the UAB, is the other corresponding author.

"These very preliminary results add to the important and growing body of knowledge on patient response to MS therapies and have the potential to positively impact MS management in the future, if confirmed in larger patient groups," noted Timon Bogumil. Bogumil is VP and head of global medical affairs for neurology, ophthalmology and hematology at the Bayer Healthcare Pharmaceuticals unit of **Bayer AG**.

"Perhaps the most exciting aspect of this work is that a simple blood test could be used to better direct treatment options in the future," said Ronald Jubin, director of R&D at **PBL InterferonSource**. "Nobody is going to dispute the importance of having a way to make sure that this expensive drug is being given to the right patients."

PBL markets research-grade IFN-related products, assays, and services.

Knowing earlier

Current methods for assessing patient responsiveness to RRMS drugs include empirical measures, such as disease relapse, or MRI to detect new disease lesions.

"If IL-17 or some other biomarker can identify early on who will and will not do well on a treatment, it would greatly benefit patients with MS," said Richard Ransohoff, director of the Neuroinflammation Research Center at the **Cleveland Clinic** and staff neurologist at its Mellen Center for Multiple Sclerosis. He also is a professor of molecular medicine at the Cleveland Clinic Lerner College of Medicine at **Case Western Reserve University**.

"Many doctors are now using MRI to see if patients are responding to their treatments because it is more sensitive than looking at relapse rate and allows treatment response to be assessed in about six months," said Alfred Sandrock, SVP of neurology research and development at **Biogen Idec Inc.** "What Steinman's work suggests is that there may be a biomarker that could be used to predict treatment responsiveness before treatment even begins."

A key next step is validating the findings in a larger cohort. Sandrock said the translational medicine group at Biogen Idec is already collaborating with Steinman's group to carry out these studies.

"We want to look at 10 to 100 times the number of serum samples that we've looked at in our paper," Steinman said.

"If the results were confirmed in a larger patient cohort, then I can imagine people would be tested to see if they are responders or non-responders to β-interferon therapy," told *SciBX*. "We have samples from patients that have been on β-interferon for years, including ones that were taken before and during treatment, so we're in a position to validate the results."

"If the results are confirmed in our retrospective analysis, or better yet in a prospective study, something like this could help doctors make better treatment decisions for their patients. You may even see such information getting added to the drug's label," added Sandrock.

Biogen Idec markets Avonex interferon beta-1a to treat relapsing forms of MS. Rebif interferon beta-1a is marketed by **Merck KGaA**.

Bayer markets interferon beta-1b as Betaseron in the U.S. and as Betaferon in the EU. Extavia, which received FDA approval last October, is **Novartis AG**'s branded version of Betaseron.

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> *—Lawrence Steinman, Stanford University*

Better than expected

A blood test that differentiates between responders and non-responders to IFN-β therapy could redirect many RRMS patients to other MS drugs.

On the flip side, both Steinman and Sandrock suggested the test could increase a responder's willingness to stay on IFN-β for longer periods of time.

"People report that β-interferon has had modest efficacy in RRMS, but that was based on clinical data from a patient population that included responders and non-responders," Steinman told *SciBX*. "If we could stratify patients based on their responsiveness to β-interferon, even retrospectively, we may find that the drug has much better efficacy than we had originally thought. This means that patients that know they are responders may be more inclined to stay on the drug even if it means having to deal with the flu-like side effects."

Sandrock noted that a refinement to the test reported in the *Nature Medicine* study could be to develop a way to distinguish between patients who respond very well to IFN-β versus those that respond but continue to have some disease symptoms. "Patients that only partially respond to interferon therapy could benefit from receiving an additional treatment," he said.

Researchers are already testing IFN-β combination therapies in several clinical trials, including the NIH-supported Phase III CombiRX trial that is evaluating Avonex plus Copaxone in people with RRMS.

Ransohoff thinks that a test for IFN-β responsiveness also could improve the design of clinical trials for new MS treatments.

However, before moving forward with the validation studies, Ransohoff pointed out that it would be important to show that the levels of these markers remain stable in individuals.

"We don't yet know how these markers fluctuate in the blood of normal people and patients," he said. "If they are stable, then you can prospectively test how well the marker predicts responsiveness to treatment. For example, you could sort MS patients into groups with high and low IL-17, start the patients on β-interferon, and see how well this predicts who develops new MRI lesions after starting treatment."

Stanford has filed a patent application covering a blood test that would distinguish between responders and nonresponders to IFN-β therapy. The work is available for licensing from the university's Office of Technology Licensing.

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